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Cuijpers, P.

published in

JAMA Psychiatry

2014

DOI (link to publisher)

[10.1001/jamapsychiatry.2014.277](https://doi.org/10.1001/jamapsychiatry.2014.277)

document version

Publisher's PDF, also known as Version of record

[Link to publication in VU Research Portal](#)

citation for published version (APA)

Cuijpers, P. (2014). Combined pharmacotherapy and psychotherapy in the treatment of mild to moderate major depression? *JAMA Psychiatry*, 71(7), 747-748. <https://doi.org/10.1001/jamapsychiatry.2014.277>

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VIEWPOINT

Combined Pharmacotherapy and Psychotherapy in the Treatment of Mild to Moderate Major Depression?

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Treatment guidelines for major depressive disorders suggest that combined treatment of pharmacotherapy and psychotherapy may be helpful in the acute phase of severe major depression.¹ However, combined treatment is not strongly recommended in mild to moderate depression. In these cases, either pharmacotherapy or psychotherapy can be used, depending on the preference of the patient, the treatment history, and other clinical factors. However, is this recommendation still supported by the current state of knowledge? In this Viewpoint, I will discuss recent evidence suggesting that combined treatment could be a first-line treatment in the acute phase of mild to moderate depressive disorders and whether this evidence is strong enough to reconsider the recommendations in treatment guidelines.

Evidence in Favor of Combined Treatment

The first piece of evidence in favor of combined treatment in mild to moderate depression is straightforward. Combined treatment is more effective than either pharmacotherapy or psychotherapy alone. Several dozens of well-designed trials and meta-analyses have clearly shown that combined treatment is superior, and that is not only the case in studies of patients with severe depression but also in studies of patients with mild to moderate depression.²

Second, both pharmacotherapy and psychotherapy probably have the most robust effects on severe depression and much smaller effects on mild to moderate depression. For pharmacotherapy, it was first suggested several years ago that effect sizes in mild to moderate depression are not clinically relevant.³ There are no validated methods available for establishing the clinical relevance of outcomes of treatments, so relevance for pharmacotherapy cannot be defined using a statistical outcome such as an effect size. However, regardless of whether treatment is clinically relevant or not, the evidence that the effects of pharmacotherapy decrease with decreasing severity is quite strong.

The evidence that psychotherapy is more effective for patients with severe depression and less so for patients with mild to moderate depression is less well established, but the evidence supporting this is increasing. It has long been thought that psychotherapy should never be used for patients with severe depression. This belief is based, in part, on the findings of the Treatment of Depression Collaborative Research Program,⁴ in which cognitive behavior therapy did not differ from placebo for more severely depressed patients, whereas antidepressant medications did. These findings suggested that pharmacotherapy was effective for severe depression

but that psychotherapy was not and should therefore only be used for mild to moderate depression.

In the same study,⁴ however, interpersonal psychotherapy was examined, and it was found that interpersonal psychotherapy did differ from placebo for patients with more severe depression, suggesting that psychological treatment can be efficacious in this population. Furthermore, meta-analytic studies have shown that it is also plausible that psychotherapy may be more effective for patients with severe depression and less effective for patients with mild to moderate depression, compared with controls.⁵ In addition, meta-analyses of studies in which psychotherapy and pharmacotherapy are directly compared with each other have found that the 2 are equally effective, regardless of baseline severity. Therefore, if pharmacotherapy is less effective against mild to moderate depression, and if psychotherapy and pharmacotherapy are equally effective against mild to moderate depression, then psychotherapy must also be less effective against mild to moderate depression.

Therefore, if it is indeed true that both work best for patients with severe depression but less well for patients with mild to moderate depression, should this not be an argument for the use of combined pharmacotherapy and psychotherapy in the treatment of mild to moderate depression? Combined treatment is more effective than either treatment alone, regardless of baseline severity. And it is well known that many patients do not respond at all or do not respond sufficiently to acute-phase treatment, and that the majority have a relapse within a couple of years after successful treatment. Aggressive treatment with the most effective interventions that are available may be the best option to improve outcome in the short and long term.

There is another argument as to why combined treatment may be the best treatment option in the acute phase of mild to moderate depression. In a recent meta-analysis,² we examined 11 trials in depression and anxiety disorders in which combined treatment, pharmacotherapy only, psychotherapy only, and placebo conditions were examined. This meta-analysis² showed again that the effects of psychotherapy and those of pharmacotherapy vs the effects of placebo were comparable. However, this study² also showed that the effects of combined treatment compared with the effects of placebo were twice as large as those of psychotherapy or pharmacotherapy only. This suggests that the effects of these 2 treatments may be independent of each other and that the effect of combined treatment is the sum of the effects of each treatment

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alone. Of course, this finding has to be considered with caution because of the confidence intervals around the effect sizes and the differences between the included studies. Functional imaging studies on depression indicate that pharmacotherapy and cognitive behavior therapy both affect the orbitofrontal cortex bilaterally and the left medial cortex but had differential effects on the cingulate cortex and the caudate in responders.⁶ These complementary effects of cognitive behavior therapy and pharmacotherapy support the notion that combined treatments may be more effective and that there is no "cannibalization" of the effects of each of the treatments. Over the past decade, an increasing proportion of patients with mental disorders received psychotropic medication without psychotherapy,⁷ and about 75% of the patients prefer psychotherapy.⁸ It can be expected that many patients will prefer combined treatment, when offered the possibility.

Arguments Against Combined Treatment

Are there arguments against combined pharmacotherapy and psychotherapy in the treatment of mild to moderate depression? Yes, there are. All treatments have advantages and disadvantages, including a risk of adverse events, side effects of medications and psychotherapy, and further deterioration during treatment. We do not have sufficient knowledge about treatments yet to predict which

treatment works best for which patient. And whether or not combined treatment should be given to patients with mild to moderate depression should not only depend on the effects found in randomized trials but also on side effects, patient preferences, costs of treatment, possible negative effects, comorbid conditions, and other clinical circumstances, such as history of depression or history of treatment. Current treatment guidelines do allow us to take such aspects into account.

Should Combined Treatment Be Recommended?

So, should combined psychotherapy or pharmacotherapy be recommended in the treatment of mild to moderate depression? The evidence shows that combined treatment is significantly more effective than either treatment alone, that they are both not very effective when applied alone but are effective when combined, and that the effects may be largely independent of each other. And currently the majority of patients receive pharmacotherapy, while they would prefer psychotherapy. It is the physician and the patient who should decide which treatment should be given to the patient, and many factors play a role in this process. However, there is no doubt that current evidence suggests that combined treatment could be a valuable treatment alternative for patients with mild to moderate depression.

ARTICLE INFORMATION

Published Online: May 7, 2014.
doi:10.1001/jamapsychiatry.2014.277.

Conflict of Interest Disclosures: None reported.

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